Complete Summary

GUIDELINE TITLE

Advanced breast cancer. Diagnosis and treatment.

BIBLIOGRAPHIC SOURCE(S)

National Collaborating Centre for Cancer. Advanced breast cancer: diagnosis and treatment. London (UK): National Institute for Health and Clinical Excellence (NICE); 2009 Feb. 25 p. (NICE clinical guideline; no. 81).

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates previous versions: National Institute for Clinical Excellence (NICE). Guidance on the use of capecitabine for the treatment of locally advanced or metastatic breast cancer. London (UK): National Institute for Clinical Excellence (NICE); 2003 May. 24 p. (Technology appraisal; no. 62).

National Institute for Clinical Excellence (NICE). Guidance on the use of vinorelbine for the treatment of advanced breast cancer. London (UK): National Institute for Clinical Excellence (NICE); 2002 Dec. 14 p. (Technology appraisal guidance; no. 54).

COMPLETE SUMMARY CONTENT

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SCOPE

DISEASE/CONDITION(S)

Advanced breast cancer: invasive adenocarcinoma of the breast of clinical stage 4

GUIDELINE CATEGORY

Counseling
Diagnosis
Evaluation
Management
Risk Assessment
Treatment

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Obstetrics and Gynecology
Oncology
Pathology
Radiation Oncology
Radiology
Surgery

INTENDED USERS

Advanced Practice Nurses
Health Care Providers
Health Plans
Managed Care Organizations
Nurses
Patients
Pharmacists
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

- To offer best practice advice on the care of patients with advanced breast cancer
- To help all those involved in the management of advanced breast cancer, including patients, carers and healthcare professionals

TARGET POPULATION

Women and men with invasive adenocarcinoma of the breast of clinical stage 4 (that is, with known metastatic disease)

Note: This guideline does not cover:

- Women and men with invasive adenocarcinoma of the breast of clinical stages 1, 2 and 3. Refer to the National Guideline Clearinghouse (NGC) summary of the National Institute for Health and Clinical Excellence (NICE) clinical guideline; no. 80 Early and locally advanced breast cancer: diagnosis and treatment
- Women and men with metastases to the breast from other primary tumours
- Women and men with rare breast tumours (for example, angiosarcoma, lymphoma)
- Women and men with benign breast tumours (for example, fibroadenoma, benign phyllodes tumours)

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis

1. Imaging assessment for disease extent and metastases
    - Plain radiography
    - Ultrasound
    - Computed tomography (CT)
    - Magnetic resonance imaging (MRI)
    - Positron emission tomography fused with computed tomography (PET-CT)
2. Pathological assessment
    - Biopsy to assess estrogen receptor (ER) status and human epidermal growth factor receptor 2 (HER2) status
3. Monitoring disease status

Management/Treatment/Counseling

1. Providing individual preference-based information and support for decision making
2. Endocrine therapy
    - Aromatase inhibitor (either non-steroidal or steroidal)
    - Tamoxifen
    - Ovarian suppression
3. Chemotherapy
    - Systemic sequential therapy
    - Combination therapy
    - Docetaxel
    - Vinorelbine
    - Capecitabine
    - Gemcitabine in combination with paclitaxel
4. Biological therapy
    - Trastuzumab
5. Supportive care
6. Managing complications
    - Managing lymphoedema
    - Managing cancer-related fatigue
    - Multidisciplinary management of uncontrolled local disease
    - Managing bone metastases
        - Bisphosphonates
        - External beam radiotherapy
    - Surgery and whole brain radiotherapy for brain metastases

MAJOR OUTCOMES CONSIDERED

- Clinical effectiveness
    - Survival (overall and progression free)
    - Response rate
    - Time to treatment failure
    - Symptom relief
    - Quality of life
    - Adverse events

- Cost effectiveness

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Collaborating Centre for Cancer (NCC-C) on behalf of the National Institute for Health and Clinical Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

Review of the Clinical Literature

At the beginning of the development phase, initial scoping searches were carried out to identify any relevant guidelines (local, national or international) produced by other groups or institutions. Additionally, stakeholder organisations were invited to submit evidence for consideration by the Guideline Development Group (GDG), provided it was relevant to the agreed list of clinical questions.

In order to answer each question the NCC-C information specialist developed a search strategy to identify relevant published evidence for both clinical and cost effectiveness. Key words and terms for the search were agreed in collaboration with the GDG. When required, the health economist searched for supplementary papers to inform detailed health economic work, for example modelling (see section on 'Incorporating Health Economic Evidence' below).

Papers that were published or accepted for publication in peer-reviewed journals were considered as evidence. Search filters, such as those to identify systematic reviews (SRs) and randomized controlled trials (RCTs) were applied to the search strategies when there was a wealth of these types of studies. No language restrictions were applied to the search; however, foreign language papers were not requested or reviewed (unless of particular importance to that question).

The following databases were included in the literature search:

- The Cochrane Library
- Medline and Premedline 1950 onwards
- Excerpta Medica (Embase) 1980 onwards
- Cumulative Index to Nursing and Allied Health Literature (Cinahl) 1982 onwards
- Allied & Complementary Medicine (AMED) 1985 onwards
- British Nursing Index (BNI) 1994 onwards
- Psychinfo 1806 onwards
- Web of Science 1970 onwards. [specifically Science Citation Index Expanded
- (SCI-EXPANDED) and Social Sciences Citation Index (SSCI)]

- System for Information on Grey Literature In Europe (SIGLE) 1980–2005
- Biomed Central 1997 onwards
- National Research Register (NRR)
- Current Controlled Trials

From this list the information specialist sifted and removed any irrelevant material based on the title or abstract before passing to the researcher. All the remaining articles were then stored in a Reference Manager electronic library.

Searches were updated and re-run 6–8 weeks before the stakeholder consultation, thereby ensuring that the latest relevant published evidence was included in the database. Any evidence published after this date was not included. For the purposes of updating this guideline, 30 June 2008 should be considered the starting point for searching for new evidence. Further details of the search strategies, including the methodological filters used, are provided in the evidence review (and appear on the accompanying CD-ROM to the original guideline).

Incorporating Health Economics Evidence

The aim of the economic input into the guideline was to inform the GDG of potential economic issues relating to advanced breast cancer. It is important to investigate whether health services are both clinically effective and cost effective, i.e., are they 'value for money'.

The health economist helped the GDG by identifying priority topics within the guideline that might benefit from economic analysis, reviewing the available economic evidence and, where necessary, conducting economic analysis. Where published economic evaluation studies were identified that addressed the economic issues for a clinical question, these are presented alongside the clinical evidence wherever possible.

In order to assess the cost-effectiveness of each priority topic, a comprehensive systematic review of the economic literature was conducted. For those clinical areas reviewed, the information specialists used a similar search strategy as used for the review of clinical evidence but with the inclusion of a health economics and quality of life filter.

Each search strategy was designed to find any applied study estimating the cost or cost effectiveness of the topic under consideration. A health economist reviewed abstracts and relevant papers were ordered for appraisal.

Published economic evidence was obtained from a variety of sources:

- Medline 1966 onwards
- Embase 1980 onwards
- NHS Economic Evaluations Database (NHS EED)
- EconLit 1969 onwards

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence for Intervention Studies

Level	Source of Evidence
1++	High-quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias.
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.
1–	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias.
2++	High-quality systematic reviews of case-control or cohort studies. High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal.
2+	Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal.
2–	Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal.
3	Non-analytic studies (for example case reports, case series).
4	Expert opinion, formal consensus.

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Collaborating Centre for Cancer (NCC-C) on behalf of the National Institute for Health and Clinical Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

Critical Appraisal and Evidence Grading

Following the literature search one researcher independently scanned the titles and abstracts of every article for each question, and full publications were obtained for any studies considered relevant or where there was insufficient information from the title and abstract to make a decision. The researcher then individually applied the inclusion/exclusion criteria to determine which studies would be relevant for inclusion and subsequent appraisal. Lists of excluded papers

were generated for each question and the rationale for the exclusion was presented to the Guideline Development Group when required.

The researcher then critically appraised the full papers. Critical appraisal checklists were compiled for each paper and one researcher undertook the critical appraisal and data extraction. The researcher assessed the quality of eligible studies by referring to the Scottish Intercollegiate Guidelines Network (SIGN) criteria for systematic reviews/meta-analyses and randomised control trials (see "Rating Scheme for the Strength of the Evidence"). Evidence relating to clinical effectiveness was classified using this established hierarchical system. However this checklist is less appropriate for studies reporting diagnostic tests of accuracy. In the absence of a validated hierarchy for this type of test, NICE suggests levels of evidence that take into account the factors likely to affect the validity of these studies.

For all the relevant appraised studies for a particular question, data on the type of population, intervention, comparator and outcomes (PICO) was recorded in evidence tables and an accompanying evidence summary prepared for the GDG (see evidence review [see "Availability of Companion Documents" field]). All the evidence was considered carefully by the GDG for accuracy and completeness.

All procedures were fully compliant with NICE methodology as detailed in the 'NICE guidelines manual'. In general, no formal contact was made with authors; however, there were ad hoc occasions when this was required in order to clarify specific details.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus
Informal Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Collaborating Centre for Cancer (NCC-C) on behalf of the National Institute for Health and Clinical Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

The Guideline Development Group (GDG)

The Advanced Breast Cancer GDG was recruited in line with the existing NICE protocol as set out in the 'NICE guidelines manual'. The first step was to appoint a Chair and a Lead Clinician. Advertisements were placed for both posts and candidates were informally interviewed prior to being offered the role. The NCC-C Director, GDG Chair and Lead Clinician identified a list of specialties that needed to be represented on the GDG. Requests for nominations were sent to the main stakeholder organisations and patient organisations/charities (see Appendix 6.2 of the full version of the original guideline document). Individual GDG members were selected by the NCC-C Director, GDG Chair and Lead Clinician, based on their application forms, following nomination from their respective stakeholder

organisation. The guideline development process was supported by staff from the NCC-C, who undertook the clinical and health economics literature searches, reviewed and presented the evidence to the GDG, managed the process and contributed to drafting the guideline.

Guideline Development Group Meetings

Fourteen GDG meetings were held between 22 June 2006 and 2 July 2008. During each GDG meeting (either held over one or two days) clinical questions and clinical and economic evidence were reviewed, assessed and recommendations formulated. At each meeting patient/carer and service-user concerns were routinely discussed as part of a standing agenda item.

NCC-C project managers divided the GDG workload by allocating specific clinical questions, relevant to their area of clinical practice, to small sub-groups of the GDG in order to simplify and speed up the guideline development process. These groups considered the evidence, as reviewed by the researcher, and synthesised it into draft recommendations prior to presenting it to the GDG as a whole. Each clinical question was led by a GDG member with expert knowledge of the clinical area (usually one of the healthcare professionals). The GDG subgroups often helped refine the clinical questions and the clinical definitions of treatments. They also assisted the NCC-C team in drafting the section of the guideline relevant to their specific topic.

Patient/Carer Members

Individuals with direct experience of advanced breast cancer services gave an integral user focus to the GDG and the guideline development process. The GDG included three patient/carer members. They contributed as full GDG members to writing the clinical questions, helping to ensure that the evidence addressed their views and preferences, highlighting sensitive issues and terminology relevant to the guideline and bringing service-user research to the attention of the GDG.

Expert Advisers

During the development phase of the guideline the GDG identified areas where there was a requirement for expert input on particular specialist clinical questions. The clinical questions were addressed by either the production of a position paper or a formal presentation by a recognised expert who had been identified via the relevant registered stakeholder organisation. A full list of recognised experts who contributed to the guideline can be found in Appendix 6.4 of the full version of the original guideline document.

All relevant position papers are presented as part of the evidence review and will also appear on the accompanying CD-ROM to this guideline.

Developing Clinical Evidence-Based Questions

An extensive list of potential topics for the guideline to investigate was compiled by the NCC-C Director and GDG Chair and Lead Clinician in consultation with a small number of breast cancer multidisciplinary teams across England and Wales.

Refer to the "Methodology" section of the full version of the original guideline document for the methods used in developing these questions.

The final list of clinical questions can be found in Appendix 5.

Linking to NICE Technology Appraisals

When this guideline was commissioned there were several published technology appraisals (TAs) and some TAs in development which were relevant to the guideline. Two methodological approaches were taken to link to these pieces of guidance.

Technology Appraisals in Development

Once the TA had been published, its recommendations were reproduced unchanged in the most appropriate section of the guideline. To ensure accurate exchange of information between the GDG and the appraisals team, a representative from the GDG attended all Appraisal Committee meetings.

Published Technology Appraisals

Published TAs are periodically reviewed to determine if they need to be updated. If the decision was taken by NICE, after consultation with stakeholders, that a TA should be updated within this guideline the GDG determined whether any new evidence had become available since the publication of the appraisal which meant the original recommendations needed to be changed. Changes to recommendations needed to be supported by cost-effectiveness analysis. Those TAs which were updated into this guideline were subject to the same methodology as all other clinical questions.

Agreeing the Recommendations

For each clinical question the GDG were presented with a summary of the clinical evidence, and where appropriate economic evidence, derived from the studies reviewed and appraised. From this information the GDG were able to derive the guideline recommendations. The link between the evidence and the view of the GDG in making each recommendation is made explicit in the accompanying qualifying statement.

Qualifying Statements

As clinical guidelines are currently formatted, there is limited scope for expressing how and why a GDG made a particular recommendation from the evidence of clinical and cost-effectiveness. To make this process more transparent to the reader, the NCC-C felt the need for an explicit, easily understood and consistent way of expressing the reasons for making each recommendation.

The way they have chosen to do this is by writing a 'qualifying statement' to accompany every recommendation and will usually cover:

- The strength of evidence about benefits and harms for the intervention being considered
- The degree of consensus within the GDG
- The costs and cost-effectiveness (if formally assessed by the health economics team)

Where evidence was weak or lacking the GDG agreed the final recommendations through informal consensus. Shortly before the consultation period, ten key priorities and five key research recommendations were selected by the GDG for implementation and the patient algorithms were agreed. To avoid giving the impression that higher grade recommendations are of higher priority for implementation, NICE no longer assigns grades to recommendations.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

Economic Modelling

In addition to the review of the relevant clinical evidence, the guideline development group (GDG) were required to determine whether or not the cost-effectiveness of each of the individual clinical questions should be investigated. After the clinical questions were decided, the GDG agreed which topics were an 'economic priority' for modelling.

Overall Relevance of the Topic

- *The number of patients affected*: interventions affecting relatively large numbers of patients were given a higher economic priority than those affecting fewer patients
- *The health benefits to the patient*: interventions that that were considered to have a potentially significant impact on both survival and quality of life were given a higher economic priority
- *The per patient cost*: interventions with potentially high financial (cost/savings) implications were given high priority compared to interventions expected to have lower financial implications
- *Likelihood of changing clinical practice*: priority was given to topics that were considered likely to represent a significant change to existing clinical practice

Uncertainty

- *High level of existing uncertainty*: higher economic priority was given to clinical questions in which further economic analysis was considered likely to reduce current uncertainty over cost-effectiveness. Low priority was given to clinical questions when the current literature implied a clearly 'attractive' or 'unattractive' incremental cost-effectiveness ratio, which was regarded as generalisable to a UK healthcare setting
- *Likelihood of reducing uncertainty with further analyses (feasibility issues)*: when there was poor evidence for the clinical effectiveness of an intervention,

then there was considered to be less justification for an economic analysis to be undertaken

Once the economic priority clinical questions had been chosen, the next task was to perform a systematic review of the cost-effectiveness literature. When relevant published evidence was identified and considered to be of sufficient quality, this information was used to inform the recommendation for that specific clinical question. When no relevant cost-effectiveness evidence was identified, or when it was not considered to be of reasonable quality, consideration was given to building a de novo economic model. This decision was made by the GDG based on an assessment of the available evidence required to populate a potential economic model.

For those clinical questions where an economic model was required, the information specialist performed supplemental literature searches to obtain additional data for modelling. Assumptions and designs of the models were explained to and agreed by the GDG members during meetings, and they commented on subsequent revisions.

The clinical questions in this guideline selected for modelling was chosen because at the time it was considered likely that the recommendations under consideration could substantially change clinical practice in the National Health Service and have important consequences for resource use. The details of the model are presented in the evidence review and Appendix 1 in the full version of the original guideline document. During the modeling process the following general principles were adhered to:

- The GDG Chair and Clinical Lead were consulted during the construction and interpretation of the model the model was based on the best evidence from the systematic review
- Model assumptions were reported fully and transparently
- The results were subject to thorough sensitivity analysis and limitations discussed
- Costs were calculated from a health services perspective

A costing report also accompanies the clinical guideline: 'Advance Breast Cancer: Costing Report is available online at www.nice.org.uk.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Consultation and Validation of the Guideline

The draft of the guideline was prepared by the National Collaborating Centre for Cancer (NCC-C) staff in partnership with the Guideline Development Group (GDG) Chair and Lead Clinician. This was then discussed and agreed with the GDG and

subsequently forwarded to the National Institute for Health and Clinical Excellence (NICE) for consultation with stakeholders.

Registered stakeholders (see Appendix 6.2 in the full version of the original guideline document) had one opportunity to comment on the draft guideline and this was posted on the NICE website between 13 August 2008 and 8 October 2008. The Guideline Review Panel also reviewed the guideline and checked that stakeholder comments had been addressed.

Following the consultation period the GDG finalised the recommendations and the NCC-C produced the final document. This was then submitted to NICE for approval and publication on their website. The other versions of the guideline (see the original guideline document and the "Availability of Companion Documents" field in this summary for more information) were also discussed and approved by the GDG and published at the same time.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Collaborating Centre for Cancer (NCC-C) on behalf of the National Institute for Health and Clinical Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

Diagnosis and Assessment

Imaging Assessment

- Assess the presence and extent of visceral metastases using a combination of plain radiography, ultrasound, computed tomography (CT) scans and magnetic resonance imaging (MRI).
- Assess the presence and extent of metastases in the bones of the axial skeleton using bone windows on a CT scan or MRI or bone scintigraphy.
- Assess proximal limb bones for the risk of pathological fracture in patients with evidence of bone metastases elsewhere, using bone scintigraphy and/or plain radiography.
- Use MRI to assess bony metastases if other imaging is equivocal for metastatic disease or if more information is needed (for example, if there are lytic metastases encroaching on the spinal canal).
- Positron emission tomography fused with computed tomography (PET-CT) should only be used to make a new diagnosis of metastases for patients with breast cancer whose imaging is suspicious but not diagnostic of metastatic disease.

Pathological Assessment

- Patients with tumours of known oestrogen receptor (ER) status whose disease recurs should not have a further biopsy just to reassess ER status.

- Patients with tumours of known human epidermal growth factor receptor 2 (HER2) status whose disease recurs should not have a further biopsy just to reassess HER2 status.
- Assess ER and HER2 status at the time of disease recurrence if receptor status was not assessed at the time of initial diagnosis. In the absence of tumour tissue from the primary tumour, and if feasible, obtain a biopsy of a metastasis to assess ER and HER2 status.

Monitoring Disease Status

- Do not use bone scintigraphy to monitor the response of bone metastases to treatment.
- Do not use PET-CT to monitor advanced breast cancer.

Providing Information and Support for Decision Making

- Assess the patient's individual preference for the level and type of information. Reassess this as circumstances change.
- On the basis of this assessment, offer patients consistent, relevant information and clear explanations, and provide opportunities for patients to discuss issues and ask questions.
- Assess the patient's individual preference for how much they wish to be involved in decision making. Reassess this as circumstances change.
- Be aware of the value of decision aids and the range available. Make the most appropriate decision aid available to the patient.

Systemic Disease-Modifying Therapy

- Offer endocrine therapy as first-line treatment for the majority of patients with ER-positive advanced breast cancer.
- Offer chemotherapy as first-line treatment for patients with ER-positive advanced breast cancer whose disease is imminently life-threatening or requires early relief of symptoms because of significant visceral organ involvement, providing they understand and are prepared to accept the toxicity.
- For patients with ER-positive advanced breast cancer who have been treated with chemotherapy as their first-line treatment, offer endocrine therapy following the completion of chemotherapy.

Endocrine Therapy

- Offer an aromatase inhibitor (either non-steroidal or steroidal) to:
    - Postmenopausal women with ER-positive breast cancer and no prior history of endocrine therapy
    - Postmenopausal women with ER-positive breast cancer previously treated with tamoxifen
- Offer tamoxifen and ovarian suppression as first-line treatment to premenopausal and perimenopausal women with ER-positive advanced breast cancer not previously treated with tamoxifen.
- Offer ovarian suppression to premenopausal and perimenopausal women who have previously been treated with tamoxifen and then experience disease progression.

- Offer tamoxifen as first-line treatment to men with ER-positive advanced breast cancer.

Chemotherapy

- On disease progression, offer systemic sequential therapy to the majority of patients with advanced breast cancer who have decided to be treated with chemotherapy.
- Consider using combination chemotherapy to treat patients with advanced breast cancer for whom a greater probability of response is important and who understand and are likely to tolerate the additional toxicity.
- For patients with advanced breast cancer who are not suitable for anthracyclines (because they are contraindicated or because of prior anthracycline treatment either in the adjuvant or metastatic setting), systemic chemotherapy should be offered in the following sequence:
    - First line: single-agent docetaxel
    - Second line: single-agent vinorelbine or capecitabine
    - Third line: single-agent capecitabine or vinorelbine (whichever was not used as second-line treatment)
- Gemcitabine in combination with paclitaxel, within its licensed indication, is recommended as an option for the treatment of metastatic breast cancer only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate.[a]

Biological Therapy

- For patients who are receiving treatment with trastuzumab[b] for advanced breast cancer, discontinue treatment with trastuzumab at the time of disease progression outside the central nervous system. Do not discontinue trastuzumab if disease progression is within the central nervous system alone.

[a] This recommendation is from 'Gemcitabine for the treatment of metastatic breast cancer', NICE technology appraisal guidance 116 (2007). It was formulated as part of that technology appraisal and not by the guideline developers. It has been incorporated into this guideline in line with NICE procedures for developing clinical guidelines, and the evidence to support the recommendation can be found at www.nice.org.uk/TA116.

[b] Recommendations on the use of trastuzumab are covered by NICE technology appraisal guidance 34 (2002) which will be updated.

Supportive Care

- Healthcare professionals involved in the care of patients with advanced breast cancer should ensure that the organisation and provision of supportive care services comply with the recommendations made in 'Improving outcomes in breast cancer: manual update' (NICE cancer service guidance [2002]) and Improving supportive and palliative care for adults with cancer' (NICE cancer service guidance [2004]), in particular the following two recommendations:
    - 'Assessment and discussion of patients' needs for physical, psychological, social, spiritual and financial support should be undertaken at key points (such as diagnosis; at commencement,

during, and at the end of treatment; at relapse; and when death is approaching).'
- 'Mechanisms should be developed to promote continuity of care, which might include the nomination of a person to take on the role of "key worker" for individual patients.'

Managing Complications

Lymphoedema

- Assess patients with lymphoedema for treatable underlying factors before starting any lymphoedema management programme.
- Offer all patients with lymphoedema complex decongestive therapy (CDT) as the first stage of lymphoedema management.
- Consider using multilayer lymphoedema bandaging (MLLB) for volume reduction as a first treatment option before compression hosiery.
- Provide patients with lymphoedema with at least two suitable compression garments. These should be of the appropriate class and size, and a choice of fabrics and colours should be available.
- Provide patients with lymphoedema with clear, written information and the contact details of local and national lymphoedema support groups.

Cancer-Related Fatigue

- Offer all patients with advanced breast cancer for whom cancer-related fatigue is a significant problem an assessment to identify any treatable causative factors, and offer appropriate management as necessary.
- Provide clear, written information about cancer-related fatigue, organisations that offer psychosocial support and patient-led groups.
- Provide information about and timely access to an exercise programme for all patients with advanced breast cancer experiencing cancer-related fatigue.

Uncontrolled Local Disease

- A breast cancer multidisciplinary team should assess all patients presenting with uncontrolled local disease and discuss the therapeutic options for controlling the disease and relieving symptoms.
- A wound care team should see all patients with fungating tumours to plan a dressing regimen and supervise management with the breast care team.
- A palliative care team should assess all patients with uncontrolled local disease in order to plan a symptom management strategy and provide psychological support.

Bone Metastases

- Consider offering bisphosphonates to patients newly diagnosed with bone metastases to prevent skeletal-related events and reduce pain.
- The choice of bisphosphonate for patients with bone metastases should be a local decision, taking into account patient preference and limited to preparations licensed for this indication.

- Use external beam radiotherapy in a single fraction of 8Gy to treat patients with bone metastases and pain.
- An orthopaedic surgeon should assess all patients at risk of a long bone fracture, to consider prophylactic surgery.

Brain Metastases

- Offer surgery followed by whole brain radiotherapy to patients who have a single or small number of potentially resectable brain metastases, a good performance status and who have no or well-controlled other metastatic disease.
- Offer whole brain radiotherapy to patients for whom surgery is not appropriate, unless they have a very poor prognosis.
- Offer active rehabilitation to patients who have surgery and/or whole brain radiotherapy.
- Offer referral to specialist palliative care to patients for whom active treatment for brain metastases would be inappropriate.

CLINICAL ALGORITHM(S)

There is a care pathway for advanced breast cancer in the quick reference guide, available at www.nice.org.uk/CG81quickrefguide. The care pathway includes algorithms for:

- Diagnosis and assessment - imaging assessment and pathological assessment
- Sequential systemic therapy - endocrine therapy - women
- Chemotherapy and biological therapy

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting the recommendations is not specifically stated.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate patient-centered care for patients with advanced breast cancer

POTENTIAL HARMS

Adverse effects of chemotherapy, biological therapy, and radiotherapy

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- This guidance represents the view of the National Institute for Health and Clinical Excellence (NICE), which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer, and informed by the summary of product characteristics of any drugs they are considering.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.
- The Guideline Development Group assumes that healthcare professionals will use clinical judgment, knowledge and expertise when deciding whether it is appropriate to apply these guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioner in light of individual patient circumstances, the wishes of the patient and clinical expertise.
- The National Collaborating Centre for Cancer disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines
- This guideline does not include recommendations covering every detail of the diagnosis and treatment of advanced breast cancer. Instead the developers have tried to focus on those areas of clinical practice that are (i) known to be controversial or uncertain; (ii) where there is identifiable practice variation; (iii) where there is a lack of high quality evidence; or (iv) where NICE guidelines are likely to have most impact. More detail on how this was achieved is presented in the section on 'Developing Clinical Evidence Based Questions' in the full version of the original guideline document.
- While every effort has been made to ensure the accuracy of the information contained within this publication, the publisher can give no guarantee for information about drug dosage and application thereof contained in this book. In every individual case the respective user must check current indications and accuracy by consulting other pharmaceutical literature and following the guidelines laid down by the manufacturers of specific products and the relevant authorities in the country in which they are practising.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

The Healthcare Commission assesses the performance of National health Service (NHS) organisations in meeting core and developmental standards set by the Department of Health in 'Standards for better health' (available from www.dh.gov.uk). Implementation of clinical guidelines forms part of the developmental standard D2. Core standard C5 says that national agreed guidance should be taken into account when NHS organisations are planning and delivering care.

NICE has developed tools to help organisations implement this guidance (listed below). These are available on the NICE website (http://guidance.nice.org.uk/CG81).

- Slides highlighting key messages for local discussion
- Costing tools
    - Costing report to estimate the national savings and costs associated with implementation
    - Costing template to estimate the local costs and savings involved
- Audit support for monitoring local practice

Key Priorities for Implementation

Diagnosis and Assessment

- Positron emission tomography fused with computed tomography (PET-CT) should only be used to make a new diagnosis of metastases for patients with breast cancer whose imaging is suspicious but not diagnostic of metastatic disease.
- Assess oestrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) status at the time of disease recurrence if receptor status was not assessed at the time of initial diagnosis. In the absence of tumour tissue from the primary tumour, and if feasible, obtain a biopsy of a metastasis to assess ER and HER2 status.

Systemic Disease-modifying Therapy

- Offer endocrine therapy as first-line treatment for the majority of patients with ER-positive advanced breast cancer.
- For patients with advanced breast cancer who are not suitable for anthracyclines (because they are contraindicated or because of prior anthracycline treatment either in the adjuvant or metastatic setting), systemic chemotherapy should be offered in the following sequence:
    - First line: single-agent docetaxel
    - Second line: single-agent vinorelbine or capecitabine
    - Third line: single-agent capecitabine or vinorelbine (whichever was not used as second-line treatment)
- For patients who are receiving treatment with trastuzumab[1] for advanced breast cancer, discontinue treatment with trastuzumab at the time of disease progression outside the central nervous system. Do not discontinue trastuzumab if disease progression is within the central nervous system alone.

[1] Recommendations on the use of trastuzumab are covered by NICE technology appraisal guidance 34 (2002) which will be updated.

Supportive Care

- Healthcare professionals involved in the care of patients with advanced breast cancer should ensure that the organisation and provision of supportive care services comply with the recommendations made in 'Improving outcomes in breast cancer: manual update' (NICE cancer service guidance [2002]) and

'Improving supportive and palliative care for adults with cancer' (NICE cancer service guidance [2004]), in particular the following two recommendations:

- 'Assessment and discussion of patients' needs for physical, psychological, social, spiritual and financial support should be undertaken at key points (such as diagnosis; at commencement, during, and at the end of treatment; at relapse; and when death is approaching).'
- 'Mechanisms should be developed to promote continuity of care, which might include the nomination of a person to take on the role of "key worker" for individual patients.'

Managing Complications

- A breast cancer multidisciplinary team should assess all patients presenting with uncontrolled local disease and discuss the therapeutic options for controlling the disease and relieving symptoms.
- Consider offering bisphosphonates to patients newly diagnosed with bone metastases, to prevent skeletal-related events and reduce pain.
- Use external beam radiotherapy in a single fraction of 8Gy to treat patients with bone metastases and pain.
- Offer surgery followed by whole brain radiotherapy to patients who have a single or small number of potentially resectable brain metastases, a good performance status and who have no or well-controlled other metastatic disease.

IMPLEMENTATION TOOLS

Audit Criteria/Indicators
Clinical Algorithm
Patient Resources
Quick Reference Guides/Physician Guides
Resources
Slide Presentation

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

End of Life Care
Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

National Collaborating Centre for Cancer. Advanced breast cancer: diagnosis and treatment. London (UK): National Institute for Health and Clinical Excellence (NICE); 2009 Feb. 25 p. (NICE clinical guideline; no. 81).

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2003 May (revised 2009 Feb)

GUIDELINE DEVELOPER(S)

National Collaborating Centre for Cancer - National Government Agency [Non-U.S.]

SOURCE(S) OF FUNDING

National Institute for Health and Clinical Excellence (NICE)

GUIDELINE COMMITTEE

Guideline Development Group

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

At the start of the guideline development process all Guideline Development Group (GDG) members' interests were recorded on a standard declaration form that covered consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared new, arising conflicts of interest which were always recorded (see Appendix 6.1 of the full version of the original guideline document for a list of disclosures).

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates previous versions: National Institute for Clinical Excellence (NICE). Guidance on the use of capecitabine for the treatment of locally advanced or metastatic breast cancer. London (UK): National Institute for Clinical Excellence (NICE); 2003 May. 24 p. (Technology appraisal; no. 62).

National Institute for Clinical Excellence (NICE). Guidance on the use of vinorelbine for the treatment of advanced breast cancer. London (UK): National Institute for Clinical Excellence (NICE); 2002 Dec. 14 p. (Technology appraisal guidance; no. 54).

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) format from the National Institute for Health and Clinical Excellence (NICE) Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Advanced breast cancer: diagnosis and treatment. Full guideline. London (UK): National Institute for Health and Clinical Excellence (NICE); 2009 Feb. 98 p. (Clinical guideline; no. 81). Electronic copies: Available in Portable Document Format (PDF) format from the National Institute for Health and Clinical Excellence (NICE) Web site.
- Advanced breast cancer. Diagnosis and treatment. Quick reference guide. London (UK): National Institute for Health and Clinical Excellence; 2009 Feb. 13 p. (Clinical guideline; no. 81). Electronic copies: Available in Portable Document Format (PDF) from the NICE Web site.
- Advanced breast cancer. Diagnosis and treatment. Audit support. London (UK): National Institute for Health and Clinical Excellence; 11 p. (Clinical guideline; no. 81). Electronic copies: Available in Portable Document Format (PDF) from the NICE Web site.
- Early and locally advanced breast cancer. Advanced breast cancer. Costing report. Implementing NICE guidance. London (UK): National Institute for Health and Clinical Excellence; 2009 Feb. 33 p. (Clinical guideline; no. 81). Electronic copies: Available in Portable Document Format (PDF) from the NICE Web site.

- Early and locally advanced breast cancer. Advanced breast cancer. Costing template. London (UK): National Institute for Health and Clinical Excellence; 2009 Feb. Various p. (Clinical guideline; no. 81). Electronic copies: Available in Portable Document Format (PDF) from the NICE Web site.
- Advanced breast cancer. Implementing NICE guidance. Slide set. London (UK): National Institute for Health and Clinical Excellence; 2009. 18 p. (Clinical guideline; no. 81). Electronic copies: Available in Portable Document Format (PDF) from the NICE Web site.
- The guidelines manual 2007. London (UK): National Institute for Health and Clinical Excellence (NICE); 2007 April. Electronic copies: Available in Portable Document Format (PDF) from the NICE Web site.

Print copies: Available from the National Health Service (NHS) Response Line 0870 1555 455. ref: N1794. 11 Strand, London, WC2N 5HR.

PATIENT RESOURCES

The following is available:

- Advanced breast cancer. Understanding NICE guidance - Information for people who use NHS services. London (UK): National Institute for Health and Clinical Excellence; 2009 Feb. 15 p. (Clinical guideline; no. 81). Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.

Print copies: Available from the National Health Service (NHS) Response Line 0870 1555 455. ref: N1795. 11 Strand, London, WC2N 5HR.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

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